REMARKS/ARGUMENTS

The office action dated March 18, 2003 has been carefully reviewed and these remarks are responsive thereto. Reconsideration and allowance of the instant application are respectfully requested

Claims 1-6, 8-14, 17-18, 21 and 24-48 remain pending in this application. Claims 1, 3, 8-10, 12-14, 18 and 21 have been amended to address the rejections under 35 U.S.C. § 112, first paragraph, correct typographical or grammatical errors and further define the invention. Claims 7, 15-16, 19-20 and 22-23 have been canceled. New claims 24-48 have been added. Support for these amendments can be found in the claims as originally filed and throughout the specification. No new matter has been added.

Rejection under 35 U.S.C. §112, second paragraph

In the Office Action, mailed March 18, 2003, claims 6, 15, 19 and 22 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 has been amended to further define R^2 and R^3 and provide antecedent basis for these claim terms used in claim 6. Support for this amendment can be found in the claims as originally filed and throughout the specification. No new matter has been added. Claims 15, 19 and 22 have been canceled. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §101

In the Office Action, claim 15, 19 and 22 were rejected under 35 U.S.C. §101 because the claimed recitation of a use without setting forth any steps involved in the process, results in an improver definition of a process. Claims 15, 19 and 22 have been canceled, and this rejection is now moot. Withdrawal is respectfully requested.

Rejections under 35 U.S.C. §103(a)

In the Office Action, claims 1, 2, 4-6, 8 and 9 were rejected under 35 U.S.C. §103(a) as being unpatentable over Marcuccio, (Patent No. WO 95/31202). This rejection is respectfully traversed. The cited document does not disclose, teach or suggest the invention claimed in claims 1, 2, 4-6, 8 and 9 or any of new claims 24-48.

Marcuccio *et al* discloses metal ion complexes (specifically Cobalt complexes) of Sarcophagine ligands for treatment of viral infections. Sarcophagine ligands of formula 2 are also generally disclosed. The Office Action acknowledges that the specific compounds exemplified in Marcuccio are not within the scope of the presently claimed invention.

With regard to the ligands of formula 2, Marcuccio indicates at page 27, lines 1-6 that those compounds may be prepared by methods described in the art. However, taking the most recent of those references, for example, Bottomley *et al.*, *Aust. J. Chem.*, 1994, 47, 143 only describes methods for preparing the compounds "Sar" [formula 2, where A1-A6 = NH; R^1, R^2 = H; R^3-R^{14} = H, and m = 1] and "Diamsar" [formula 2, where A1-A6 = NH; R^1, R^2 = NH_3; R^3-R^{14}

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= H, and m = 1], and salts thereof. According to Bottomley *et al*, Diamsar was obtained from the corresponding cobalt complex using (i) concentrated HCl in a bomb apparatus with heating; or refluxing HBr (page 148). Sar was obtained by heating an aqueous solution with NaCN (page 150-151).

The Bottomley reference states at page 145 (final paragraph) that:

"The cobalt(II) complexes themselves ... have an extraordinarily high stability and inertness to dissociation of the metal ion... The removal of the ligand is therefore not a trivial matter, and some time has been devoted to developing methods of extruding the metal ion from the cage... We report herein details of these extrusion processes..."

The above noted syntheses are the results of the attempts by the authors to remove cobalt from the Sarcophagine cage structure. There is no teaching of how to obtain functionalized Sarcophagine ligands of formula (I) of the present invention in the Bottomley reference, or in Marcuccio. Indeed, the comments of Bottomley *et al* and the stringent reaction conditions attest to the difficulty encountered in obtaining metal free ligands, even for the most simple of the Sarcophagine cage structures.

In contrast to Marcuccio, the present invention provides metal free Sarcophagine ligands of formula (I) which are functionalized at at least one apical position with a chemically active linker group ("Z") which is capable of binding the compound of formula (I) to a Molecular Recognition Unit (MRU), such as an antibody. There is no teaching or suggestion in Marcuccio

to functionalize the apical position of the sarcophagine cage with such a linker group. Moreover, in light of the comments of Bottomley *et al* (as referenced in Marcuccio) in regard to the difficulty of removing metal ions from the Sarcophagine cage structure, it is believed a skilled person would not have had a reasonable expectation of being able to obtain the metal free ligands from such functionalized cryptate metal complexes.

Applicants have surprisingly found that metal free cryptate ligands of formula (I) can be prepared which are functionalized with a chemically reactive linker group at either or both of the apical positions of the cage structure, which allow the compounds to be conjugated to a molecular recognition unit. The present invention enables a range of metal ion complexes to be prepared, including radiolabelled metal ions with short half-lives.

As disclosed in the present application (e.g., Schemes 1 and 2 on pages 16 and 17 of the specification), compounds of formula (I) are prepared by forming a metal ion complex of Diamsar using a metal ion, such as copper (which can later be removed by reducing with $NaBH_4$ in the presence of Pd/C). The copper Diamsar metal complex is then functionalized at the apical amino group(s) with an appropriate "linker" (group "Z" in formula (I)), after which the copper is removed using $NaBH_4$/Pd/C, without any apparent degradation of the cage structure, to provide the metal free functionalized Sarcophagine ligand. The functionalized ligand can then be conjugated to an MRU through the chemically reactive linker group. After the ligand has been conjugated to the MRU, the ligand-MRU conjugate can be converted to a metal complex, including radionuclides. The present invention is advantageous for radionuclides which have a

short half-life, or for radionuclides with a very long half-life to which minimal exposure is required.

Another unexpected advantage of the ligands of formula (I) according to the present invention is that the ligands possess exceptional complexation behavior. For instance, Example 2 (page 18) of the present specification shows that complete complexation with ^{64}Cu was achieved within 1 minute for all pH $\geq$ 4.0. In addition, the stability of the radiocomplexes at low concentrations (see Example 3) represents a significant advantage for use in diagnostic and therapeutic applications.

Accordingly, the present claims are not obvious in view of Marcuccio.

In the Office Action, claims 1, 2, 4-6 and 8-23 were rejected under 35 U.S.C. §103(a) as being unpatentable over Marcuccio (Patent No. WO 95/31202) in view of Alvarez (Patent No. 4,741,900). This rejection is respectfully traversed. The cited documents, either alone or in combination, do not disclose, teach or suggest the invention claimed in claims 1, 2, 4-6 and 8-23 or any of new claims 24-48.

The Office Action states that "...it is known in the art that cryptate compounds may be radiolabelled to provide an effective radiopharmaceutical for both therapeutic and diagnostic use". However, in relation to claims 1, 2 and 4-6, Marcuccio *et al* does not teach or enable the preparation of the free-base Sarcophagine ligands of formula (I) according to the present invention. There is no teaching or motivation to combine the cited references. Moreover, in view of the difficulty and stringent reaction conditions for removing cobalt from simple Sarcophagine

ligands, (see for example Bottomley *et al* at pages 148-150; and Behm *et al* at page 1014, final paragraph *et seq.*), it is submitted that obtaining other metal free Sarcophagine ligands would not have been an obvious or trivial process, as indicated by the comments in Bottomley *et al* discussed above. In any event, Marcuccio does not teach or suggest preparation of Sarcophagine ligands which are functionalized with at least one chemically active linker group capable of conjugating the ligand to an MRU as claimed.

With regard to claims 8-23, it is submitted that a person skilled in the art having read Marcuccio in view of Alvarez, would not have been led to the metal complexes as presently claimed. Firstly, as discussed above, Marcuccio does not enable synthesis of the metal free ligands of formula (I). Secondly, Alvarez teaches formation of metal ion complexes by "*attaching the metal ion directly to the chelator*" [col. 13; lines 55-64]. Thus, Alvarez only teaches the formation of metal ion complexes and radioactive metal ion complexes by chelating the metal ion to a metal free ligand. As discussed above, obtaining metal free cryptate compounds is not considered a trivial matter by persons skilled in the art (see the comments in Bottomley *et al* discussed above). Thirdly, Alvarez only exemplifies forming metal ion complexes of DTPA chelators [col. 20, line 41 to col. 23, line 32]. Alvarez does not teach or suggest formation of metal ion complexes of Cryptates.

Accordingly, the present claims are not obvious in view of Marcuccion and/or Alvarez.

Allowable Subject Matter

In the Office Action, claims 3 and 7 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants thank the Examiner for the notice of Allowable subject matter. Claims 3 and 7 have been rewritten in independent form as new claims 43 and 30, respectively. Claim 3 also has been amended to correct the typographical error noted by the Office Action, and the claim now ends with a period.

CONCLUSION

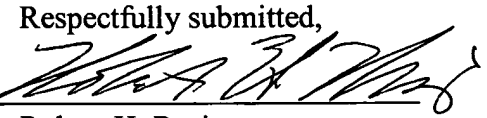
In view of the above amendments and remarks, prompt reconsideration and full allowance of the claims pending in the subject application are respectfully requested. All rejections having been addressed, applicant respectfully submits that the instant application is in condition for allowance, and respectfully solicits prompt notification of the same.

The Commissioner is authorized to debit or credit our Deposit Account No. 19-0733 for any fees due in connection with the filing of this response.

If the Examiner should have any questions, the Examiner is invited to contact the undersigned at the number set forth below.

Respectfully submitted,

Date: August 18, 2003

By: 

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